ORIGINAL ARTICLE: EARLY PREGNANCY

Postmolar gestational trophoblastic neoplasia: beyond the traditional risk factors

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Objective: To investigate the slope of linear regression of postevacuation serum hCG as an independent risk factor for postmolar gestational trophoblastic neoplasia (GTN).
Design: Multicenter retrospective cohort study.
Setting: Academic referral health care centers.
Patient(s): All subjects with confirmed hydatidiform mole and at least four measurements of β-hCG titer.
Intervention(s): None.
Main Outcome Measure(s): Type and magnitude of the relationship between the slope of linear regression of β-hCG as a new risk factor and GTN using Bayesian logistic regression with penalized log-likelihood estimation.
Result(s): Among the high-risk and low-risk molar pregnancy cases, 11 (18.6%) and 19 cases (13.3%) had GTN, respectively. No significant relationship was found between the components of a high-risk pregnancy and GTN. The β-hCG return slope was higher in the spontaneous cure group. However, the initial level of this hormone in the first measurement was higher in the GTN group compared with in the spontaneous recovery group. The average time for diagnosing GTN in the high-risk molar pregnancy group was 2 weeks less than that of the low-risk molar pregnancy group. In addition to slope of linear regression of β-hCG (odds ratio [OR], 12.74, confidence interval [CI], 5.42–29.2), abortion history (OR, 2.53; 95% CI, 1.27–5.04) and large uterine height for gestational age (OR, 1.26; CI, 1.04–1.54) had the maximum effects on GTN outcome, respectively.
Conclusion(s): The slope of linear regression of β-hCG was introduced as an independent risk factor, which could be used for clinical decision making based on records of β-hCG titer and subsequent prevention program. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: GTN, human chorionic gonadotropin, independent risk factor, penalized logistic regression

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Gestational trophoblastic disease (GTD), a group of disorders identified by abnormal proliferation of trophoblastic tissue, is one of the prognoses of spontaneous recovery, local invasion, and metastasis. The general term of gestational trophoblastic neoplasia (GTN) is used to describe a wide range of malignant trophoblastic diseases including invasive mole, choriocarcinoma, epithelioid trophoblastic tumor, and placental site trophoblastic tumor (1, 2). Although GTN is generally seen in molar pregnancies, it can be seen in any pregnancy.

Although hydatidiform mole is generally diagnosed in the first trimester of pregnancy during routine pregnancy tests, its clinical signs and symptoms are rarely seen at this time (3). According to current available definitions, this neoplasia is confirmed by the following criteria: [1] no decrease in hCG levels over four consecutive measurements, [2] an increase in hCG serum titer measured over 3 consecutive weeks, [3] detectable hCG serum

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titer 6 months after evacuation of molar pregnancy, and [4] histological diagnosis of choriocarcinoma (4–6). Data reveal that about 18%–28% of molar pregnancies lead to a sustainable neoplasia (5). Different designs and populations have been used across the world to study this disorder, with no standard definition for the cases; furthermore, the data used in this field have not generally been collected for research purposes (7). Therefore, reporting the incidence of this neoplasia in a manner by which it can precisely represent the studied populations, whether in Iran or other countries, is a problematic process; this is the reason for the significant differences in the incidence reported from different regions of the world (4, 8, 9). GTN is usually seen after a molar pregnancy, emphasizing the importance of identifying the risk factors of molar pregnancy (10). The traditional risk factors of this malignant disease include professional jobs, abortion history, intervals between pregnancies (11), hormonal changes, early menarche, and contraceptives (12, 13). Studies have reported a significant relationship between uterine height larger for gestational age and prior molar pregnancy and an increased risk for GTN (14). Another study has reported only a relationship associated with serum titer >100,000 mIU/mL as the cutoff (15).

There are very few systematic studies documented that provide a well-elucidated insight into GTN risk factors and introduce newer indicators for it in particular. Attempts to predict this neoplasia are generally based on the hCG indicator (level 2 prevention). In practice, identification of the risk factors and intervention into their mechanisms and biology with the aim of preventing this disease have been overlooked. Using a new and reliable indicator, this study aimed at specifying GTN risk factors to reduce its risk and burden.

MATERIALS AND METHODS

Study Population

This multicenter retrospective cohort study evaluated all documents of patients with hydatidiform mole who were referred to educational and treatment centers between 2003 and 2013 (10 years) and whose illness was confirmed by pathological tests carried out during hospitalization and follow-up. Data of partial and complete hydatidiform mole with at least four measurements of β-hCG titer were included in the study. After identifying the prevalence of different GTDs, the study excluded [1] patients with no useful data owing to having inappropriate follow-ups or test result records, [2] patients whose hCG level was not measured at most within 48 hours after evacuation, [3] patients who received prophylactic chemotherapy before mole evacuation, and [4] patients who had undergone hysterectomy.

To this end, the files of 98,658 births from 2003 to 2013 were studied and 221 cases of molar pregnancy were identified; of these nine, three, and eight cases were excluded owing to receiving coprophlaxi drugs, having had initial hysterectomy treatments, or having incomplete files with irrelevant information, respectively. Among the qualified patients (n = 201), 31 had GTN, and the serum hormone level in the remaining cases had spontaneously returned to normal values during follow-up practices. In the present study, high-risk molar pregnancy was defined according to the following criteria: [1] initial titer of β-hCG hormone >100,000 mIU/mL, [2] uterine height larger than 2 weeks for gestational age, and [3] theca lutein cyst bigger than 6 cm.

Evaluation and Immunoassays

According to current literature, in all treatment centers, the first titer of β-hCG was measured and recorded at most 48 hours after evacuation of molar pregnancy (16). The follow-up procedure was as follows: in all cases with molar pregnancy, titration was perfomed on a weekly basis until three consecutive normal titers were obtained. After normalization of titers, the procedure was performed on a monthly basis for 6 months.

All measurements of β-hCG in serum were performed with sensitive and specific RIAs, developed in our laboratories based on polyclonal antibodies raised in rabbits; the RIAs of β-hCG have been described elsewhere (17). In the RIA for β-hCG, a highly purified hCG β-subunit preparation labeled with iodine-125 (NaI^{125}, Amersham plc) was used as a tracer. The RIAs were calibrated with the third International Standard (IS) preparations for intact hCG or the hCG α- or hCG β-subunits (WHO third IS hCG 75/537, hCGα 75/569, or hCG β 75/551, respectively).

Statistical Analysis

Basic demographic and clinical continuous data are shown as mean and SD, while grouped data are shown in the form of frequency and percentage. Chi-square or Fisher's exact tests were used to show whether the two categorical variables are independent. Since the distribution of β-hCG concentration was not normal in the beginning, it was normalized by transforming the scale to a natural logarithm. The main variable studied for determining GTN risks was the β-hCG concentration regression line slope. Therefore, the data were reshaped from wide to long, after which the β-hCG concentration regression line slope was calculated by Stata, using four recorded measurements for each case. The Fracpoly model was also used to determine the type of relationship between the main variable, that is, β-hCG concentration logarithm slope, and outcome; this model was used owing to the continuous nature of β-hCG in serum as well as the disadvantages of converting continuous to categorical data. The relevant details of the model have been published elsewhere (18–20). For estimation of GTN-associated risk factors odds ratio (ORs), Bayesian logistic regression with penalized likelihood estimation was used to control for confounding variables. Confounding variables were selected in accordance with the backward method, by studying to what extent the addition or elimination of the variables changes ORs between risk factor and outcome. Application of the models in discrete data with low population size has been discussed before (21, 22). The method of Kaplan–Meier was used to show the time of GTN diagnosis in high- and low-risk molar pregnancies. All analyses were performed by Stata 12. The proposal of this project was approved by the Institutional Review Board of Shahid Beheshti University of Medical Sciences.